Change in correspondence address.

Applicants note that a Revocation and Substitute Power of Attorney incorporating a change in correspondence address was filed on April 30, 2001. For the convenience of the Examiner, a copy of this document is enclosed. In accordance with the instructions provided therein, Please direct all future correspondence regarding the subject application to CUSTOMER NUMBER 22798, that is:

22798

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Sequence Listing Rules.

The Examiner indicated that the application is not in compliance with sequence rules, 37 C.F.R. §§ 1.821-1.825. In particular, the examiner noted that errors were to be found in the sequence listing previously filed.

A substitute sequence listing is provided herewith. In particular, a disk containing the referenced sequence(s) in computer readable form, and a paper copy of the sequence information that has been printed from the floppy disk are provided herewith. The sequences identified in the sequence listing introduce no new matter and are found in the application as originally filed. The information contained in the computer readable disk is identical to that of the paper copy.

Election/Restriction.

In the Office Action of February 16, 2001, the Examiner required restriction to one of the following "supergroups":

SuperGroup A:	Claims 1-9, and 18-23 drawn to a nucleic acid encoding any one of the 49 C-1027 biosynthesis polypeptides, vectors and host cells;
SuperGroup B:	Claims 10-14, drawn to the entire gene cluster which encodes polypeptides sufficient to direct the assembly of C-1027 or analogues thereof;
SuperGroup C:	Claims 15-17, drawn to any one of the 49 C-1027 biosynthesis polypeptides;

SuperGroup D:	Claims 24-50, drawn to methods of chemically modifying a biological molecule using any one of the 49 C-1027 biosynthesis polypeptides;
SuperGroup E:	Claims 51-53, drawn to methods of synthesizing a chromaprotein type enediyne core using particular polypeptides;
SuperGroup F:	Claims 54-56, drawn to methods of synthesizing a deoxysugar using particular polypeptides;
SuperGroup G:	Claims 57-60, drawn to methods of synthesizing a beta amino acid using particular polypeptides;
SuperGroup H:	Claims 61-68, drawn to methods of synthesizing an enediyne or analogue thereof using the C-1027 biosynthetic gene cluster; and
SuperGroup I:	Claims 69-71, drawn to methods of making a cell resistant to enediyne or analogue thereof using polynucleotides encoding particular polypeptides.

In addition, the Examiner indicated that SuperGroups A, C, or D, are elected Applicants must elect a particular open reading frame (ORF-7 through 42) for prosecution. With election of SuperGroup B or H, the claims are examined requiring that all ORFs be present. With election of SuperGroup E or F election of ORFs 17, 20, 21, 29, 30, 32, 35, or 38 is required. With election of SuperGroup I, one of ORFs 9, 2, 27, 0, 1 (c-terminus and n-terminus), or 2 must be elected for prosecution.

In response to this restriction, Applicants provisionally elect SuperGroup D, (claims 24-50), Group 135 (ORF 28) with traverse.

A) Restriction within each SuperGroup is legally Improper.

Applicants note, however that **the restriction within SuperGroups A through I is legally improper.** In making such a restriction, the Examiner effectively requires that a single claim (*e.g.,* claim 1, claim 24, *etc.*) be divided up and presented in several applications. This flatly contravenes accepted law. As stated by the CCPA:

> As a general proposition, an applicant has a right to have ***each claim*** examined on the merits.
>
> * * *
>
> If, however, a single claim is required to be divided up and presented in several applications, that claim would never be considered on the merits. The totality of the resulting fragmentary claims would not necessarily be the equivalent of the original claim. Further, since the subgenera would be defined by the examiner, rather than by the applicant, it is not inconceivable that a number of the fragments would not be described in the specification.
>
> * * *

> §121 provides the Commissioner with the authority to promulgate rules designed to *restrict* an *application* to one of several claimed inventions, ... It does not provide a basis under the authority of the Commissioner to *reject* a particular *claim* on that same basis.
>
> * * *
>
> We hold that a rejection under §121 violates the basic right of the applicant to claim his invention as he chooses. *In Re Weber, Soder and Boksay* 198 USPQ 328, 331-332 (CCPA 1978)

See also, *In Re Haas* 179 USPQ 623, 624, 625 (*In Re Haas I*) and *In Re Haas* 198 USPQ 334-337 (*In Re Haas II*).

The CCPA thus recognized that an Examiner **may not** reject a particular claim on the basis that it represents "independent and distinct" inventions. *See, In re Weber Soder and Boksay, supra.* Moreover, **the CCPA recognized that imposition of a restriction requirement on a single claim is just such an improper rejection.**

In particular, the courts have definitively ruled that the statute authorizing restriction practice, *i.e.*, 35 U.S.C. §121, provides no legal authority to impose a restriction requirement on a single claim, even if the claim presents multiple independently patentable inventions. *See, In Re Weber, Soder and Boksay, In Re Haas I, and In Re Haas II.* More specifically, the CCPA expressly ruled that there is no statutory basis for rejecting a claim for misjoinder, despite previous attempts by the Patent Office to fashion such a rejection. As noted in *Weber*:

> The discretionary power to limit one applicant to one invention is no excuse at all for refusing to examine a broad generic claim-- **no matter how broad, which means no matter how many independently patentable inventions may fall within it**. [emphasis added] *In Re Weber* at 334.

Applicants recognize that instead of improperly imposing a restriction requirement on a single claim, the Office may limit initial examination to a "reasonable number" of species encompassed by the claim. *See*, 37 C.F.R. §1.146. This practice strikes an appropriate balance between the concerns of the patent office regarding administrative concerns and unduly burdensome examination, and the clear constitutional and statutory rights of an inventor to claim an invention as it is contemplated, provided the dictates of 35 U.S.C. §112 are complied with. *See, e.g.*, the MPEP at 803.02, *In Re Wolfrum* 179 USPQ 620 (CCPA, 1973) and *In re Kuehl* 177 USPQ 250 (CCPA, 1973). Unlike a restriction requirement, a species election does not preclude an applicant from pursuing the original

form of a claim in subsequent prosecution, nor does it force an applicant to file multiple divisional applications that are incapable of capturing the intended scope of the application. It should be clear that the added cost of filing and prosecuting **178 divisional patent applications** in the present case ***does not*** strike an appropriate balance between the administrative concerns of the office and Applicants statutory rights as an inventor.

Finally, Applicants note that the CCPA has explicitly held that improper restriction of a single claim is a decision under the jurisdiction of the Board of Appeals, and the Federal Courts. This is in contrast to simple administrative decisions regarding ordinary restriction requirements, which are not generally subject to Appellate review. *See, In Re Haas I, supra.* Because restriction of a single claim into multiple groups is tantamount to a rejection and a refusal to examine the claim as drafted, as articulated in *Haas I*, the Board of Appeals and the courts have jurisdiction over the decision. Accordingly, **Applicants expressly reserve the right to appeal any decision that may be made regarding the present petition to the Patent Office Board of Appeals and to the Federal Circuit**.

B) Restriction within SuperGroup D is particular improper.

Applicants further note that restriction to particular open reading frames (ORFs) within SuperGroup D is particularly egregious.

Claim 24 of SuperGroup D is drawn to:

> 24. A method of chemically modifying a biological molecule, said method comprising contacting a biological molecule that is a substrate for a polypeptide encoded by a C-1027 biosynthesis gene cluster open reading frame, with a polypeptide encoded by a C-1027 biosynthesis gene cluster open reading frame whereby said polypeptide chemically modifies said biological molecule.

While claim 26 of the same SuperGroup recites:

> 26. The method of claim 24, wherein said method comprising contacting said biological molecule with **at least two different polypeptides** encoded by C-1027 biosynthesis gene cluster open reading frames.

The Examiners insistence that examination of SuperGroup D be limited to a single Open Reading Frame, **in effect renders examination of dependent claim 26 impossible** since claim 26 recites at least two different C-1027 polypeptides (ORFS). Under the proposed restriction scheme, claim 26 cannot be examined.

This is precisely the result the Federal Circuit sought to avoid. As stated in *Weber,* such "a rejection under §121 violates the basic right of the applicant to claim his invention as he chooses." The Examiner's restriction within SuperGroup D is thus legally improper and should be withdrawn.

If a telephone conference would expedite prosecution of this application, the Examiner is invited to telephone the undersigned at (510) 337-7871.

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APPENDIX A

VERSION WITH MARKINGS TO SHOW CHANGES MADE IN 09/478,188 WITH ENTRY OF THIS AMENDMENT

In the specification:

For type II PKS, the following two pairs of degenerate primers were used—5'-AGC TCC ATC AAG TCS ATG RTC GG-3' (forward, SEQ ID NO:~~103~~102) / 5'-CC GGT GTT SAC SGC GTA GAA CCA GGC G-3' (reverse, SEQ ID NO:~~104~~103) and 5'-GAC ACV GCN TGY TCB TCV-3' (forward, SEQ ID NO:~~105~~104)/5'-RTG SGC RTT VGT NCC RCT-3' (SEQ ID NO:~~106~~105) (B, C+G+T; N, A+C+G+T; R, A+G; S, C+G; V, A+C+G; Y, C+T) (reverse) (Seow *et al.* (1997) *J. Bacteriol.,* 179: 7360-7368). No product was amplified under all conditions tested. For type I PKS, the following pair of degenerate primers were used—5'-GCS TCC CGS GAC CTG GGC TTC GAC TC-3' (forward, SEQ ID NO:~~107~~106) / 5'-AG SGA SGA SGA GCA GGC GGT STC SAC-3' (S, G+C) (reverse, SEQ ID NO:~~108~~107) (Kakavas *et al.* (1997) *J. Bacteriol.,* 179: 7515-7522). A distinctive product with the predicted size of 0.75 kb was amplified in the presence of 20% glycerol and cloned into pGEM-T according to the protocol provided by the manufacturer (Promega) to yield pBS1001.

For NGDH, the following pair of degenerate primers were used 5'-CS GGS GSS GCS GGS TTC ATC GG-3' (forward, SEQ ID NO:~~109~~108) / 5'-GG GWR CTG GYR SGG SCC GTA GTT G-3' (R, A+G; S, C+G; W, A+T; Y, C+T) (reverse, SEQ ID NO:~~110~~109) (Decker, *et al.* (1996) FEMS Lett., 141: 195-201). A distinctive product with the predicted size of 0.55 kb was amplified and cloned into pGEM-T to yield pBS1002.

For *cagA*, the following pair of primers, flanking its coding region, were used—5'-AG GTG GAG GCG CTC ACC GAG-3' (forward, SEQ ID NO:~~111~~110)/5'-G GGC GTC AGG CCG TAA GAA G-3' (reverse, SEQ ID NO:~~112~~111) (Sakata *et al.* (1992) *Biosci. Biotechnol. Biochem.,* 56: 159201595). A distinctive product with the predicted size of 0.73 kb was amplified from pBS1005 and cloned into pGEM-T to yield pBS1003.

In the claims:

APPENDIX B

CLAIMS PENDING IN USSN 09/478,188 WITH ENTRY OF THIS AMENDMENT

1. An isolated nucleic acid comprising a nucleic acid selected from the group consisting of

a nucleic acid encoding any of C-1027 open reading frames (ORFs) -7 through 42, excluding ORF 9 (cagA);

a nucleic acid encoding a polypeptide encoded by any of C-1027 open reading frames (ORFs) -7 through 42, excluding ORF 9 (cagA); and

a nucleic acid amplified by polymerase chain reaction (PCR) using primer pairs that amplify any of C-1027 open reading frames (ORFs) -7 through 42, excluding ORF 9 (cagA).

2. The isolated nucleic acid of claim 1, wherein said nucleic comprises a nucleic acid encoding at least two open reading frames (ORFs) selected from the group consisting of ORF-1 through ORF 42, excluding ORF 9 (cagA).

3. The isolated nucleic acid of claim 1, wherein said nucleic comprises a nucleic acid encoding at least three open reading frames (ORFs) selected from the group consisting of ORF-1 through ORF 42, excluding ORF 9 (cagA).

4. An isolated nucleic acid comprising a nucleic acid that specifically hybridizes under stringent conditions to an open reading frame (ORF) of the C-1027 biosynthesis gene cluster, excluding ORF 9 (cagA), and can substitute for the ORF to which it specifically hybridizes to direct the synthesis of an enediyne.

5. The isolated nucleic acid of claim 4, wherein said isolated nucleic acid comprises a nucleic acid that specifically hybridizes under stringent conditions to a nucleic acid selected from the group consisting of ORF -7, ORF -6, ORF -5, ORF -4, ORF -3, ORF -2, ORF -1, ORF 0, ORF 1, ORF 2, ORF 3, ORF 4, ORF 5, ORF 6, ORF 7, ORF 8, ORF 10, ORF 11, ORF 12, ORF 13, and ORF 14.

6. The isolated nucleic acid of claim 4, wherein said isolated nucleic acid comprises a nucleic acid that specifically hybridizes under stringent conditions to a nucleic acid selected from the group consisting of ORF 15, ORF 16, ORF 17, ORF 18, ORF 19, ORF 20, ORF 21, ORF 22, ORF 23, ORF 24, ORF 25, ORF 26, ORF 27, ORF 28, ORF 29, ORF 30, ORF 31, ORF 32, ORF 33, ORF 34, ORF 35, ORF 36, ORF 37, ORF 38, ORF 39, ORF 40, ORF 41, and ORF 42.

7. The isolated nucleic acid of claim 5, wherein said isolated nucleic acid comprises a nucleic acid selected from the group consisting of ORF -7, ORF -6, ORF -5, ORF -4, ORF -3, ORF -2, ORF -1, ORF 0, ORF 1, ORF 2, ORF 3, ORF 4, ORF 5, ORF 6, ORF 7, ORF 8, ORF 10, ORF 11, ORF 12, ORF 13, and ORF 14.

8. The isolated nucleic acid of claim 6, wherein said isolated nucleic acid comprises a nucleic acid selected from the group consisting of ORF 15, ORF 16, ORF 17, ORF 18, ORF 19, ORF 20, ORF 21, ORF 22, ORF 23, ORF 24, ORF 25, ORF 26, ORF 27, ORF 28, ORF 29, ORF 30, ORF 31,

ORF 32, ORF 33, ORF 34, ORF 35, ORF 36, ORF 37, ORF 38, ORF 39, ORF 40, ORF 41, and ORF 42.

9. The isolated nucleic acid of claim 4, wherein said nucleic acid comprises a nucleic acid that is a single nucleotide polymorphism (SNP) of a nucleic acid selected from the group consisting of ORF -7, ORF -6, ORF -5, ORF -4, ORF -3, ORF -2, ORF -1, ORF 0, ORF 1, ORF 2, ORF 3, ORF 4, ORF 5, ORF 6, ORF 7, ORF 81, ORF 1, ORF 2, ORF 3, ORF 4, ORF 5, ORF 6, ORF 7, ORF 8, ORF 10, ORF 11, ORF 12, ORF 13, ORF 14, ORF 15, ORF 16, ORF 17, ORF 18, ORF 19, ORF 20, ORF 21, ORF 22, ORF 23, ORF 24, ORF 25, ORF 26, ORF 27, ORF 28, ORF 29, ORF 30, ORF 31, ORF 32, ORF 33, ORF 34, ORF 35, ORF 36, ORF 37, ORF 38, ORF 39, ORF 40, ORF 41, and ORF 42.

10. An isolated gene cluster comprising open reading frames encoding polypeptides sufficient to direct the assembly of a C-1027 enediyne or a C-1027 enediyne analogue.

11. The gene cluster of claim 10, wherein said gene cluster is present in a bacterium.

12. The gene cluster of claim 11, wherein said gene cluster is present in a bacterium selected from the group consisting of Actinomycetes, Actinoplanetes, Actinomadura, Micromonospora, and Streptomycetes.

13. The gene cluster of claim 11, wherein said gene cluster is present in a bacterium selected from the group consisting Streptomyces globisporus, Streptomyces lividans, Streptomyces coelicolor, Micromonospora echinospora spp. calichenisis, Actinomadura verrucosopora, Micromonospora chersina, Streptomyces carzinostaticus, and Actinomycete L585-6.

14. The gene cluster of claim 13, wherein one or more open reading frames is operatively linked to a heterologous promoter.

15. An isolated polypeptide comprising a catalytic domain encoded by a nucleic acid of a C-1027 gene cluster wherein said nucleic acid comprises a nucleic acid selected from the group consisting of

a nucleic acid encoding any of C-1027 open reading frames (ORFs) -7 through 42, excluding ORF 9 (cagA); and

a nucleic acid amplified by polymerase chain reaction (PCR) using any one of the primer pairs identified in Tables I and II that specifically amplify one or more of (ORFs) -7 through 42, excluding ORF 9 (cagA).

16. The polypeptide of claim 15, wherein said polypeptide is encoded by at least two open reading frames selected from the group consisting of C-1027 open reading frames (ORFs) -7 through 42, excluding ORF 9 (cagA).

17. The polypeptide of claim 15, wherein said polypeptide is encoded by at least three open reading frames selected from the group consisting of C-1027 open reading frames (ORFs) -7 through 42, excluding ORF 9 (cagA).

18. An expression vector comprising a nucleic acid of any one of claims 1 through 9.

19. A host cell transformed with an expression vector of claim 18.

20. The host cell of claim 19, wherein said cell is transformed with an exogenous nucleic acid comprising a gene cluster encoding polypeptides sufficient to direct the assembly of a C-1027 enediyne or a C-1027 enediyne analogue.

21. The host cell of claim 19, wherein said host cell is a bacterium.

22. The host cell of claim 21, wherein said bacterium is selected from the group consisting of Actinomycetes, Actinoplanetes, Actinomadura, Micromonospora, and Streptomycetes.

23. The host cell of claim 21, wherein said bacterium is selected from the group consisting of Streptomyces globisporus, Streptomyces lividans, Streptomyces coelicolor, Micromonospora echinospora spp. calichenisis, Actinomadura verrucosopora, Micromonospora chersina, Streptomyces carzinostaticus, and Actinomycete L585-6.

24. A method of chemically modifying a biological molecule, said method comprising contacting a biological molecule that is a substrate for a polypeptide encoded by a C-1027 biosynthesis gene cluster open reading frame, with a polypeptide encoded by a C-1027 biosynthesis gene cluster open reading frame whereby said polypeptide chemically modifies said biological molecule.

25. The method of claim 24, wherein said polypeptide is an enzyme selected from the group consisting of a hydroxylase, a homocysteine synthase, a dNDP-glucose dehydrogenase, a citrate carrier protein, a C-methyl transferase, an N-methyl transferase, an aminotransferase, a CagA apoprotein, an NDP-glucose synthase, an epimerase, an acyl transferase, a coenzyme F390 synthase, and epoxidase hydrolase, an anthranilate synthase, a glycosyl transferase, a monooxygenase, a type II condensation protein, an aminomutase, a type II adenylation protein, an O-methyl transferase, a P-450 hydroxylase, an oxidoreductase, and a proline oxidase.

26. The method of claim 24, wherein said method comprising contacting said biological molecule with at least two different polypeptides encoded by C-1027 biosynthesis gene cluster open reading frames.

27. The method of claim 24, wherein said method comprising contacting said biological molecule with at least three different polypeptides encoded by C-1027 biosynthesis gene cluster open reading frames.

28. The method of claim 24, wherein said contacting is in a host cell.

29. The method of claim 28, wherein said host cell is a bacterium.

30. The method of claim 24, wherein said contacting ex vivo.

31. The method of claim 28, wherein said biological molecule is an endogenous metabolite produced by said host cell.

32. The method of claim 28, wherein said biological molecule is an exogenous supplied metabolite.

33. The method of claim 28, wherein said host cell is a eukaryotic cell.

34. The method of claim 33, wherein said eukaryotic cell is selected from the group consisting of a mammalian cell, a yeast cell, a plant cell, a fungal cell, and an insect cell.

35. The method of claim 28, wherein said host cell synthesizes sugars and glycosylates the biological molecule.

36. The method of claim 35, wherein said host cell synthesizes deoxysugars.

37. The method of claim 24, wherein said method further comprises contacting said biological molecule with a polyketide synthase or a non-ribosomal polypeptide synthetase.

38. The method of claim of claim 24, wherein said contacting is in a bacterial cell.

39. The method of claim of claim 24, wherein said contacting is ex vivo.

40. The method of claim 24, wherein said method comprises contacting said biological molecule with at substantially all of the polypeptides encoded by C-1027 biosynthesis gene cluster open reading frames and said method produces an enediyne or enediyne analogue.

41. The method of claim 24, wherein said biological molecule is a fatty acid and said biological molecule is contacted with a C-1027 orf polyeptide selected from the group consisting of an epoxide hydrase, a monooxygenase, an iron-sulfer flavoprotein, a p-450 hydroxylase, an oxidoreductase, and a proline oxidase.

42. The method of claim 41, wherein said biological molecule is a fatty acid and said biological molecule is contacted with a plurality of C-1027 orf polypeptides comprising an epoxide hydrase, a monooxygenase, an iron-sulfer flavoprotein, a p-450 hydroxylase, an oxidoreductase, and a proline oxidase.

43. The method of claim 42, wherein said biological molecule is contacted with polypeptides encoded by ORF17, ORF20, ORF21, ORF29, ORF30, ORF32, ORF35, and ORF38.

44. The method of claim 41, wherein said biological molecule is contacted with polypeptides encoded by ORF 15, ORF 16, ORF 28, ORF3, ORF 14, and ORF 13.

45. The method of claim 44 wherein said biological molecule is also contacted with polypeptides encoded by ORF 4 and ORF 3.

46. The method of claim 24, wherein said method comprises contacting a sugar with one or more C-1027 open reading frame polypeptides selected from the group consisting of a dNDP-glucose synthase, a dNDP glucose dehydratase, an epimerase, an aminotransferase, a C-methyltransferase, an N-methyltransferase, and a glycosyl transferase.

47. The method of claim 46, wherein said method comprises contacting a dNDP-glucose with a plurality of C-1027 open reading frame polypeptides comprising a dNDP-glucose synthase, a dNDP glucose dehydratase, an epimerase, an aminotransferase, a C-methyltransferase, an N-methyltransferase, and a glycosyl transferase.

48. The method of claim 24, wherein said method comprises contacting an amino acid with one or one or more C-1027 open reading frame polypeptides selected from the group consisting of a hydroxylase, an aminomutase, a type II NRPS condensation enzyme, a type II NRPS adenylation enzyme, and a type II peptidyl carrier protein.

49. The method of claim 48, wherein said method comprises contacting an amino acid with a plurality of C-1027 open reading frame polypeptides comprising a hydroxylase, a halogenase, an aminomutase, a type II NRPS condensation enzyme, a type II NRPS adenylation enzyme, and a type II peptidyl carrier protein.

50. The method of claim 48, wherein said amino acid is a tyrosine.

51. A method of synthesizing a chromaprotein type enediyne core, said method comprising contacting a fatty acid with one or more C-1027 orf polypeptides selected from the group consisting of an epoxide hydrase, a monooxygenase, an iron-sulfer flavoprotein, a p-450 hydroxylase, an oxidoreductase, and a proline oxidase.

52. The method of claim 51, wherein said fatty acid is contacted with a plurality of C-1027 orf polypeptides comprising an epoxide hydrase, a monooxygenase, an iron-sulfer flavoprotein, a p-450 hydroxylase, an oxidoreductase, and a proline oxidase.

53. The method of claim 52, wherein said fatty acid is contacted with polypeptides encoded by ORF17, ORF20, ORF21, ORF29, ORF30, ORF32, ORF35, and ORF38.

54. A method of synthesizing a deoxysugar, said method comprising contacting a sugar with one or more C-1027 open reading frame polypeptides selected from the group consisting of a dNDP-glucose synthase, a dNDP glucose dehydratase, an epimerase, an aminotransferase, a C-methyltransferase, an N-methyltransferase, and a glycosyl transferase.

55. The method of claim 54, wherein said method comprises contacting a dNDP-glucose with a plurality of C-1027 open reading frame polypeptides comprising a dNDP-glucose synthase, a dNDP glucose dehydratase, an epimerase, an aminotransferase, a C-methyltransferase, an N-methyltransferase, and a glycosyl transferase.

56. The method of claim 55, wherein said dNDP-glucose is contacted with polypeptides encoded by ORF17, ORF20, ORF21, ORF29, ORF30, ORF32, ORF35, and ORF38.

57. A method of synthesizing a beta amino acid, said method comprising contacting an amino acid with one or one or more C-1027 open reading frame polypeptides selected from the group consisting of a hydroxylase, an aminomutase, a type II NRPS condensation enzyme, a type II NRPS adenylation enzyme, and a type II peptidyl carrier protein.

58. The method of claim 57, wherein said method comprises contacting an amino acid with a plurality of C-1027 open reading frame polypeptides comprising a hydroxylase, a halogenase, an aminomutase, a type II NRPS condensation enzyme, a type II NRPS adenylation enzyme, and a type II peptidyl carrier protein.

59. The method of claim wherein said amino acid is contacted with polypeptides encoded by ORF 4, ORF11, ORF24, ORF23, ORF25, and ORF26.

60. The method of claim 57, wherein said amino acid is a tyrosine.

61. A method of synthesizing an enediyne or an enediyne analogue said method comprising:

culturing a cell comprising a recombinantly modified C-1027 gene cluster under conditions whereby said cell expresses said enediyne or enediyne analogue; and

recovering said enediyne or enediyne analogue.

62. The method of claim 61, wherein said gene cluster is present in a bacterium.

63. The gene cluster of claim 62, wherein said gene cluster is present in a bacterium selected from the group consisting of Actinomycetes, Actinoplanetes, Actinomadura, Micromonospora, and Streptomycetes.

64. The gene cluster of claim 62, wherein said gene cluster is present in a bacterium selected from the group consisting Streptomyces globisporus, Streptomyces lividans, Streptomyces coelicolor, Micromonospora echinospora spp. calichenisis, Actinomadura verrucosopora, Micromonospora chersina, Streptomyces carzinostaticus, and Actinomycete L585-6.

65. The method of claim 61, wherein said gene cluster is present in a eukaryotic cell.

66. The method of claim 65, wherein said eukaryotic cell is selected from the group consisting of a mammalian cell, a yeast cell, a plant cell, a fungal cell, and an insect cell.

67. The method of claim 61, wherein said host cell synthesizes sugars and glycosylates said enediyne or enediyne analogue.

68. The method of claim 67, wherein said host cell synthesizes deoxysugars.

69. A method of making a cell resistant to an enediyne or an enediyne metabolite, said method comprising expressing in said cell one or more isolated C-1027 open reading frame nucleic acids that encode a protein selected from the group consisting of a CagA apoprotein, a SgcB transmembrane efflux protein, a transmembrane transport protein, a Na+/H+ transporter, an ABC transport, a glycerol phosphate tranporter, and a UvrA-like protein.

70. The method of claim 69, wherein said isolated C-1027 open reading frame nucleic acids are selected from the group consisting of ORF 9, ORF2, ORF 27, ORF 0, ORF 1 c-terminus, ORF 2, and ORF 1 N-terminus.

71. The method of claim 69, wherein said cell is a bacterial cell.